Levo(-) amphetamine and dextro(+) amphetamine in the treatment of narcolepsy

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SUMMARY   The narcoleptic syndrome is a life-long and sometimes familial disorder in which there is a disturbance of the rapid eye movement phase of sleep. Patients with periodic sleep in the day-time but no other symptoms seldom develop the narcoleptic syndrome and have a separate unrelated disorder. Twelve patients with the narcoleptic syndrome were treated separately with l(−) amphetamine and d(+) amphetamine. Both drugs abolished narcolepsy, d(+) amphetamine being slightly more potent than l(−) amphetamine. In equipotent doses, unwanted effects of nervousness and insomnia were equal in frequency. No tolerance to either preparation developed during a six month period. Cataplexy was not affected by amphetamine treatment, but was abolished in two patients when clomipramine was given together with either amphetamine.

The treatment of narcolepsy by amphetamines was established by Prinzmetal and Bloomberg in 1935. As a high dosage is often required, toxic effects occur which include insomnia, nervousness, tremor, hypertension, hyperpyrexia and, rarely, acute paranoid psychosis (Connell, 1958). Amphetamine tolerance and addiction, however, are uncommon (Goodman and Gilman, 1970). Evidence has been presented which indicates that d(+) amphetamine is twice as potent as the racemic mixture of d(+) and l(−) amphetamine, suggesting that l(−) amphetamine itself is inactive (Martindale and Westcott, 1967). L(−) amphetamine has, however, been used successfully by Passouant and his colleagues to treat patients with narcolepsy who have not responded to d(+) amphetamine or in whom this isomer caused dose-limiting unwanted effects (Passouant *et al.*, 1964; Schwab and Passouant, 1964). Because of this apparent controversy and as the two amphetamine isomers have different biochemical and behavioural effects (Snyder *et al.*, 1970; Taylor and Snyder, 1970), we have re-investigated the use of d(+) and l(−) amphetamine in treating patients with the narcoleptic syndrome.

CLINICAL DIAGNOSTIC CRITERIA
(modified from Yoss and Daly, 1957)

NARCOLEPSY   Periodic and frequently irresistible sleep in the day-time which may occur at inappropriate times and is often produced by monotony.

CATAPLEXY   Loss of voluntary movement produced by emotion or sudden startle which results in head nodding, immobility, collapse, or double vision.

SLEEP PARALYSIS   Paralysis of voluntary movements on waking from sleep.

HYPNAGOGIC HALLUCINATIONS   Vivid and commonly visual sensory impressions, often frightening, which occur during half-sleep.

METHODS

PATIENTS   Five male and seven female patients with the narcoleptic syndrome were studied aged 28–59 (mean, 40) years. Five were male and seven female, 11 were Caucasian, and one male was African. They had been untreated previously or could tolerate

withdrawal of medication. The patients found it difficult to give an accurate subjective account of the frequency and duration of their sleep attacks, which were confirmed by witnessed accounts in eight patients. Untreated patients had from two to 11 narcoleptic attacks each day (mean, seven) lasting from 5 to 60 minutes (mean, 19 minutes). Sleep attacks were most frequent during the afternoon and evening and many occurred while travelling, reading, watching television, sitting, or eating. Eight patients also had cataplexy. In these head nodding was common, occurring daily in two patients. Momentary immobility was less common and complete lapses of posture with falling were rare, occurring at most one or two times each month. Three patients had episodic double vision with laughter, one of whom described horizontal object separation. A further patient complained of episodic difficulty in focusing with ptosis. Five patients, four of whom had cataplexy, also had hypnagogic hallucinations which included visions of falling through space and of being chased, dreams of concentration camps, and the desolation of war. Eight patients had infrequent sleep paralysis.

No patient had a family history of the narcoleptic syndrome, but the paternal uncle of one patient suffered from narcolepsy without other features. None suffered from chronic bronchitis or other respiratory illness and there was no history of abnormal thirst or obesity. The findings on clinical examination of all patients were normal and no patient had blackouts or showed electroencephalographic features suggesting epilepsy.

MEDICATION *Pre-trial medication* Three patients were taking d(+) amphetamine sulphate (10, 15, and 20 mg/day respectively) and another took methylphenidate (60 mg/day) before this trial. Their treatment was stopped for one week and the patients were warned of possible drowsiness. All complained of an increased number of narcoleptic attacks during this withdrawal period and one patient complained of considerable increase in appetite.

Phase I—l(−) amphetamine and placebo The activity of l(−) amphetamine was compared with placebo during a three week period. All patients took a placebo preparation in the first week. Either l(−) amphetamine or placebo was given in the second week (double-blind) and the order of administration was reversed in the third week. The dose of l(−) amphetamine was 40 mg daily in 10 mg capsules taken at 7.30, 12, 15.30, and 19.30 hours. Placebo capsules contained maize stearate (BP) 10 mg, lactose (BP) 335 mg, and magnesium stearate (BP) 5 mg.

Phase II—Relative potencies of l(−) amphetamine and d(+) amphetamine The relative potency of 20 mg of each amphetamine isomer was determined during the following two weeks. Each was given separately (double-blind) in two divided doses of 10 mg taken at 7.30 and 12.00 hours for one week followed by a week of the other medication. Five patients gave a subjective preference for l(−) amphetamine and seven for d(+) amphetamine.

Phase III—Long-term l(−) amphetamine and d(+) amphetamine therapy Each patient was given the amphetamine isomer they preferred in the comparison above. The optimum dosage was established and found to be: levoamphetamine 20–60 mg/day, dextroamphetamine 10–45 mg/day.

PATIENT ASSESSMENT On clock-face diagrams patients recorded the onset and duration of day and night sleep periods during each Tuesday and Thursday. They noted cataplexy, sleep paralysis, hypnagogic hallucinations, and double vision and stated the treatment period preferred. Unwanted side-effects including tremor, nervousness, palpitations, and insomnia were recorded, and the blood pressure, pulse rate, and temperature were recorded at weekly intervals during the trial.

ELECTROENCEPHALOGRAPHIC RECORDINGS The electroencephalogram (EEG) was recorded twice on eight patients during placebo and levoamphetamine treatment at 15.30–16.30 hr. Electrode placement and recording techniques were standardized and the onset and duration of sleep-periods were determined from the first 40 minutes of recording period by the methods of Rechtschaffen and Kales (1968).

URINARY AMPHETAMINE DETERMINATION A 24 hour urine sample taken during the period of l(−) amphetamine treatment was analysed for l(−) and d(+) amphetamine content. The method used was the gas–liquid chromatographic separation of l(−) and d(+) amphetamine from urine after derivatization with the optically active reagent N-trifluoro-acetyl-L-propyl chloride to form a distereoisomeric pair (Beckett and Tester, 1972).

CLOMIPRAMINE TREATMENT OF CATAPLEXY Cataplexy did not respond to either amphetamine isomer. Two patients who were disabled by this symptom were given clomipramine 25 mg twice daily together with d(+) amphetamine (2·5 mg/day) in one patient and l(−) amphetamine (10 mg/day) in the other.

RESULTS

L(−) AMPHETAMINE AND PLACEBO The fre-
quency and duration of narcoleptic attacks
during periods of placebo treatment and in un-
treated patients were similar. L(−) amphetamine
40 mg/day reduced the frequency of these attacks
(P < 0·01); there were none in nine patients and a
reduced occurrence in both frequency and dura-
tion in the other three (Table 1). Cataplexy,
hypnagogic hallucinations, and double-vision
were all reported to approximately the same
extent during both placebo and l(−) amphet-
amine treatment.

TABLE 1

RESPONSE OF PATIENTS WITH NARCOLEPSY TO PLACEBO AND
L(−) AMPHETAMINE 40 MG/DAY

	Pre-trial no medication	Placebo	L(−) amphet-amine
Patients (no.)	12	12	12
Observations (no.)	24	48	24
Narcoleptic attacks			
Per day (no.)	7 ± 0·45	8 ± 0·47	2·9 ± 0·37*
Duration (min)	19 ± 2·9	20 ± 3·0	15 ± 4·9
Mean nightly sleep (hr)	7·5 ± 0·37	7·75 ± 0·37	6·5 ± 0·37

Mean values ± 1SEM.
* l(−) amphetamine better than placebo, P < 0·01.

Eleven patients gave a subjective preference
for the l(−) amphetamine period compared with
placebo and one patient had no preference. All
were taking l(−) amphetamine during the
appropriate period as shown by the gas–liquid
chromatographic results. D(+) amphetamine
was not detected in the urine samples. The un-
wanted effects reported are shown in Table 2.
Five patients complained of insomnia while on
l(−) amphetamine. Nervousness, sweating, and
palpitations were recorded during both placebo

TABLE 2

UNWANTED EFFECTS OF AMPHETAMINE TREATMENT*

	Placebo	L(−) amphetamine (40 mg/day)	L(−) amphetamine (20 mg/day)	D(+) amphetamine (20 mg/day)
Insomnia	0	5	0	3
Nervousness	5	4	0	2
Sweating	1	1	1	0
Palpitation	1	1	0	1
Tremor	0	1	1	3

* The number of patients complaining of each side-effect is shown.

and l(−) amphetamine treatment. There was no
significant change in mean pulse rate, body
temperature, or blood pressure, during either the
initial l(−) amphetamine treatment or at the
end of six months.

COMPARISON OF L(−) AMPHETAMINE AND D(+)
AMPHETAMINE D(+) amphetamine was slightly
more effective than l(−) amphetamine in abolish-
ing narcolepsy, but this difference was not
statistically significant (P > 0·05). Three patients
had narcoleptic attacks on both amphetamines, a
further three patients had no attacks while taking
dextroamphetamine, and six reported no narco-
leptic attacks with either isomer (Table 3). Cata-

TABLE 3

RESPONSE OF PATIENTS WITH NARCOLEPSY TO L(−)
AMPHETAMINE AND D(+) AMPHETAMINE 20 MG/DAY

	L(−) amphetamine (20 mg/day)	D(+) amphetamine (20 mg/day)
Narcoleptic attacks/day (no.)	2·1 ± 0·43	1·4 ± 0·31
Duration of narcoleptic attack (min)	15 ± 3·9	15 ± 2·4
Total night sleep period (hr)	8·7 ± 0·41	8·7 ± 0·43

Mean values ± 1SEM. The mean differences between l(−) amphet-
amine and d(+) amphetamine are not significant (P > 0·05).

plexy, hypnagogic hallucinations, and double-
vision were not affected by either preparation;
sleep paralysis was not recorded during this
trial. Seven patients gave a subjective preference
for d(+) amphetamine and five patients for l(−)
amphetamine at the end of this phase.

LONG-TERM AMPHETAMINE THERAPY The daily
number of narcoleptic attacks at the end of a six
month treatment period with either l(−)
amphetamine or d(+) amphetamine was similar
to that in phase II. One patient required adjust-
ment of l(−) amphetamine dosage during this
six month period, increasing after three months
from 40 to 50 mg/day. No new side-effects were
reported.

ELECTROENCEPHALOGRAPHIC RECORDING Every
patient went to sleep during both placebo and
l(−) amphetamine treatment (Table 4). The
majority of time was spent in stages 1 and 2 of
sleep. Stages 3 and 4 were rare, as was rapid eye

TABLE 4

EEG CHANGES IN PATIENTS WITH NARCOLEPSY

	Placebo	L(−) amphetamine
Wakefulness (W)	12·1	10·1
Total sleep time (TST)	27·9	29·9
Stage of sleep		
I	14·2	8·5
II	16·0	19·5
III	1·0	2·7
IV	0	0·1
REM sleep	0·6	1·1
Latency of onset of sleep (min)	10·9	5·8

Mean duration of wakefulness and sleep periods (min) in eight patients with the narcoleptic syndrome. Sleep latency defined as interval between recording onset and first occurrence of 1 min stage I or deeper sleep. No difference between placebo and l(−) amphetamine treatment period is significant (P > 0·05, Wilcoxon's signed rank test).

movement (REM) sleep, which occurred in only three subjects, during the l(−) amphetamine period in one patient and during placebo treatment in two. The first type of sleep in every patient was stage 1 and never REM. The latency of onset of sleep was very variable during both placebo and l(−) amphetamine treatment (range on placebo 0–33·7 minutes; on l(−) amphetamine 0–21 minutes).

CLOMIPRAMINE TREATMENT OF CATAPLEXY Clomipramine abolished cataplexy in the two patients to whom it was given. Both of these previously had occasional sleep paralysis and hypnagogic hallucinations which also responded to this treatment. Clomipramine had no beneficial affect upon narcolepsy and caused slight persistent drowsiness at the commencement of treatment. Blood pressure and pulse rate were not changed by the addition of clomipramine.

DISCUSSION

The narcoleptic syndrome of drowsiness, cataplexy, sleep-paralysis, and hypnagogic hallucinations is not uncommon, but all four symptoms are present in only a third of patients (Wolfenden, 1969). Double vision or momentary focusing difficulty with ptosis is sometimes the only evidence of cataplexy. The syndrome is a life-long disorder and the prognosis for recovery is poor (Prull, 1963). Both narcolepsy and cataplexy are occasionally familial; only one of the present patients had an affected relative (Daly and Yoss, 1959; Gelardi and Brown, 1967). Narcolepsy has

been described in patients with disseminated sclerosis and a variety of tumours of the nervous system which are mainly in the periventricular grey matter and neighbouring parts of the diencephalon and mesencephalon (Berg and Hanley, 1963; Tridon *et al.*, 1969).

However, in most of these cataplexy was not present or narcolepsy was an incidental finding. Some patients with narcolepsy also have epilepsy (Symonds, 1954), but in those described here, neither epilepsy nor evidence of structural damage to the nervous system was present. The familial occurrence, absence of constant pathological basis, and lifelong nature of the narcoleptic syndrome is consistent with a specific biochemical disorder.

The REM phase of sleep is abnormal in patients with the narcoleptic syndrome (Rechtschaffen *et al.*, 1963). Night sleep starts with a REM phase. This suggests that the narcoleptic syndrome is unrelated to the condition of excess drowsiness without other symptomatology. The latter patients have normal REM sleep and rarely develop the narcoleptic syndrome (Passouant *et al.*, 1968). Amphetamines suppress REM sleep (Rechtschaffen and Marron, 1964), and this may account for their action in narcolepsy, rather than any stimulant effect on the central nervous system; phenelzine which abolishes REM sleep also abolishes narcolepsy (Wyatt *et al.*, 1971). Despite the action of l(−) amphetamine in reducing the frequency of narcoleptic attacks, the EEG evidence suggests that the drug has no effect on the EEG patterns of narcoleptic diurnal sleep.

The precise relationship between narcolepsy and cataplexy is uncertain, but there is a reduction in muscle tone during sleep and particularly in REM sleep (Hishikawa *et al.*, 1965). Stimulation of closely related centres in the animal brain produces either REM sleep or muscular paralysis (Jouvet and Delorme, 1965).

However, during an attack of cataplexy, the patient is clearly not asleep and the EEG record shows wakefulness (Hishikawa and Kaneko, 1965). This distinction between narcolepsy and cataplexy is shown also by the action of amphetamine on the first and clomipramine on the second.

Amphetamines affect catecholamine stores in the central nervous system (Carlsson *et al.*, 1965),

but each isomer has a different effect. D(+) amphetamine is 10 times as potent as l(−) amphetamine in inhibiting the accumulation of noradrenaline in nerve terminals, but both forms are equiactive on dopamine accumulation in selected brain regions (Taylor and Snyder, 1970). D(+) amphetamine is 10 times as potent as l(−) amphetamine in causing motor hyperactivity in rats, but only one to two times as potent in causing stereotyped behaviour (Snyder et al., 1970). This agrees with the view that dopamine rather than noradrenaline is associated with stereotyped behaviour, while hypermotility may be related more to noradrenaline (Randrup and Scheel-Krüger, 1966). The relative potency of the amphetamine isomers in narcolepsy would thus be consistent with an action on cerebral dopamine rather than on noradrenaline. However, the toxic effects of both amphetamines mimic those of adrenaline, since anxiety, restlessness, palpitations, and tremor occur and not nausea and vomiting. Both drugs control narcolepsy, though, as they may have a different therapeutic index, if toxic symptoms result from d(+) amphetamine, l(−) amphetamine is worth trial. If cataplexy is disabling, the addition of imipramine or clomipramine is often successful (Akimoto et al., 1960; Passouant et al., 1970).

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